A Meta-Analysis of Bladder Cancer and Diesel Exhaust Exposure

Paolo Boffetta[1,2] *Debra T. Silverman*[2]

The aim of this study is to review and summarize the available epidemiologic studies of bladder cancer and occupational exposure to diesel exhaust. We retrieved relevant studies and abstracted their characteristics and results. We assessed the heterogeneity of the results to decide whether to perform a fixed-effects model meta-analysis. We identified 35 relevant studies. No overall meta-analysis was performed because of heterogeneity in results. Results of railroad workers (N = 14) suggested an increased occurrence of bladder cancer, but we did not conduct a meta-analysis. The summary relative risk (RR) among truck drivers was 1.17 (95% confidence interval [CI] = 1.06–1.29, 15 studies) and that among bus drivers was 1.33 (95% CI = 1.22–1.45, 10 studies). Ten studies considered diesel exhaust exposure based on a job exposure matrix or a similar approach; the summary RR for these studies was 1.13 (95% CI = 1.00–1.27). A positive dose-response relation was suggested by 10 of the 12 studies that provided relevant information. The summary RR for high diesel exposure was 1.44 (95% CI = 1.18–1.76). There was some evidence of publication bias, however, with a lack of small studies with null or negative results. Our review suggests that exposure to diesel exhaust may increase the occurrence of bladder cancer, but the effects of misclassification, publication bias, and confounding cannot be fully taken into account. (Epidemiology 2001;12: 125–130)

Keywords: bladder neoplasms, diesel exhaust, occupation, meta-analysis.

Several studies have addressed the possible increase in cancer occurrence among workers exposed to diesel engine exhausts.[1] The lung is likely to be the main target organ of the toxic effects of diesel exhaust, and the available epidemiologic evidence points toward a summary RR of about 1.3.[2] For other organs, such as the larynx, pancreas, bladder, and kidney, the suspicion exists of an increased incidence of cancer following exposure to diesel exhaust.[1,3] In particular, an effect on the urinary bladder is plausible because metabolites of polycyclic and nitro-polycyclic aromatic hydrocarbons present in diesel exhaust are concentrated in the urine and may interact with the urothelium of the bladder.[4]

Various types of exposure to diesel exhaust have been investigated. Some studies were conducted among groups of highly exposed workers, such as drivers. In other studies, workers were classified according to probability or intensity of exposure to diesel exhaust on the basis of either a job-exposure matrix (JEM) or the assessment of job histories by a group of experts.

We conducted a review of the available results of epidemiologic studies of the association between occupational exposure to diesel exhaust and occurrence of urinary bladder cancer. Our aims were to summarize available results, to address the sources of heterogeneity in the results, and to address the possible role of chance, bias, confounding and differences in study methods.

Methods

We searched the epidemiologic literature for studies concerning cancer occurrence after exposure to diesel exhaust and for studies on occupational risk factors of bladder cancer. We also surveyed the list of references of identified articles and reviews for secondary references. We included studies published in peer-reviewed journals as well as studies reported in publications from public health authorities, such as Departments of Health. We concentrated on five occupational groups: (1) railroad workers (engine workers whenever possible), (2) bus garage maintenance workers, (3) truck drivers, (4) bus drivers, and (5) operators of heavy machines in ground and road construction; we also considered (6) studies providing a classification of exposure to diesel exhaust based on a JEM or on experts' assessment of individual occupational histories.

Most studies reported only one measure of association

From [1]Unit of Environmental Cancer Epidemiology, International Agency for Research on Cancer, Lyon, France; and [2]Occupational Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD.

Address correspondence to: Paolo Boffetta Unit of Environmental Cancer Epidemiology International Agency for Research on Cancer 150 cours Albert-Thomas 69008 Lyon, France.

Submitted April 18, 2000; Final version accepted July 24, 2000.

TABLE 1. Cohort Studies Included in the Meta-Analysis (Results Refer to Men and Are Not Adjusted for Smoking unless Stated Otherwise)

Study	Country	Design Aspects	Exposure	RR	95% CI
Rushton *et al*, 1983[13]	UK	Mo	Bus garage workers	1.39	[0.72–2.43]
Howe *et al*, 1983[14]	Canada	Mo	Railroad workers	1.03	[0.88–1.20]
Schenker *et al*, 1984[15]	USA	Mo	Railroad workers	0.76	0.15–2.21
Wong *et al*, 1985[16]	USA	Mo	HEO*	1.18	0.78–1.72
Boffetta *et al*, 1988[17]	USA	Mo, S	JEM*	1.04	[0.55–1.78]
Gustavsson *et al*, 1990[18]	Sweden	I, MW	Bus garage workers	0.66	0.18–1.68
Soll-Johanning *et al*, 1998[19]	Denmark	I, MW	Bus drivers	1.4 M	1.2–1.6
				1.3 W	0.2–4.7

* Result with a corresponding RR for high exposure (Table 5).
I, incidence; Mo, mortality; MW, men and women; S, adjusted for smoking; HEO, heavy equipment operators; JEM, job-exposure matrix; RR, relative risk; CI, confidence interval. Results in squared brackets were derived from raw data reported in the publication.

(rate ratio, odds ratio, or other) for bladder cancer, typically referring to employment in the diesel exhaust-exposed occupation for a period of at least 6 months or 1 year. Some investigations, however, also reported results for different groups of exposed workers, usually classified according to duration of employment or according to probability or intensity of exposure.

Some of the results of the studies we identified overlapped. When the overlap was due to an update or expansion of a previous study, we used only the report with the largest study base and did not reference the previous reports. When the same group of workers was used in more than one analysis with different definitions of exposure (for example results based on a JEM and results for individual occupations included in the JEM), we used the report with the broadest exposure category for the analysis of any exposure to diesel exhaust.

TABLE 2. Case-Control Studies Included in the Meta-Analysis (Results Refer to Mean and are Adjusted for Smoking unless Stated Otherwise)

Study	Country	Design aspects	Exposure	RR	95% CI
Decoufle *et al*, 1977[20]	USA	I	Truck drivers	[1.67]	[0.94–2.98]
			Bus drivers	[2.89]	[0.86–9.73]
			Railroad workers	[1.63]	[0.66–4.04]
Howe *et al*, 1980[21]	Canada	I	Railroad workers*	9.0	1.2–395
			JEM	2.8	0.8–11.8
Silverman *et al*, 1983[22]	USA	I	Truck drivers*	2.1	[1.2–3.7]
			Bus drivers*	1.5	0.4–5.3
			Truck drivers with self-reported exposure	11.9	1.4–4.4
Schoenberg *et al*, 1984[23]	USA	I, NS	Truck drivers*	1.06	0.76–1.48
			Bus drivers	1.17	0.63–2.17
Hoar & Hoover, 1985[24]	USA	Mo	Truck drivers†	1.5	0.9–2.6
			JEM*†	1.5	0.8–2.8
Vineis & Magnani, 1985[25]	Italy	I, NS	Truck drivers	1.2	0.6–2.5
			Railroad workers	0.5	0.2–1.4
Wynder *et al*, 1985[26]	USA	I	JEM†	0.87	0.47–1.58
			Truck, bus drivers*	0.9	0.4–1.9
			Railroad workers*	2.0	0.3–11.6
			HEO*	0.7	0.2–3.5
Silverman *et al*, 1986[4]	USA	I	Truck drivers†	1.3	0.9–1.9
			Bus drivers†	1.3	1.1–1.4
Jensen *et al*, 1987[27]	Denmark	I, MW	Truck, bus drivers†	1.29§	1.05–1.59
Iscovich *et al*, 1987[28]	Argentina	I, MW	Railroad workers, drivers	[4.16]	[1.82–9.53]
Risch *et al*, 1988[29]	Canada	I	Railroad workers	1.07	0.71–1.61
			JEM	1.53	1.17–2.00
		W	JEM	0.62	0.23–1.57
Bonassi *et al*, 1989[30]	Italy	I, MW	Truck drivers	1.88	0.44–8.00
Kunze *et al*, 1992[31]	Germany	I	Railroad workers	3.0	1.0–8.8
			Truck drivers	1.8	1.1–2.8
Cordier *et al*, 1993[32]	France	I	JEM	0.99	0.32–3.03
			Railroad workers	0.80	0.49–1.30
Siemiatycki *et al*, 1994[33]	Canada	I	Experts' assessment†	1.0	0.6–1.4
			Truck drivers*	1.2	0.8–1.9
Porru *et al*, 1996[34]	Italy	I	Truck drivers	1.1	0.5–2.2

* Overlapping category not used in the analysis of exposure to any source of diesel exhaust.
† Result with a corresponding RR for high exposure (Table 5).
§ 10+ years of employment.
I, incidence; Mo, mortality; MW, men and women; NS, not adjusted for smoking; HEO, heavy equipment operators; JEM, job-exposure matrix; RR, relative risk; CI, confidence interval. Results in squared brackets were derived from raw data reported in the publication.

TABLE 3. Studies Based on Routinely Collected Data Included in the Meta-Analysis, Men*

Study	Milham, 1976[35]	Coggon *et al*, 1984[36]	Gallagher *et al*, 1989[37]	Hrubec *et al*, 1992[38]	Dolin & Cook-Mozaffari 1992[39]	Pukkala, 1995[40]
Country	USA	UK	Canada	USA	UK	Finland
Exposure data	DC	DC	DC	MR	DC	Census
Railroad workers	0.78 0.53–1.11		0.69 0.33–1.28		1.61† 0.85–2.75	1.35*§ 0.85–2.05
HEO			1.79 1.02–2.91		1.64† 0.79–3.02	
Truck drivers	1.40 1.00–1.89		0.96 0.64–1.38	1.1 0.55–2.13	1.08† 0.88–1.32	0.98 0.79–1.19
Bus drivers	0.91 0.29–2.12		1.40 0.78–2.32	3.1 1.21–8.12	0.81† 0.44–1.36	
JEM		1.0¶ 0.7–1.3			1.06 0.88–1.26	

* In each cell, relative risk and 95% confidence interval are presented.
† Overlapping category not used in the analysis of exposure to any source of diesel exhaust.
§ Relative risk 11.5 (95% confidence interval = 1.39–41.5) among women.
¶ Result with a corresponding relative risk for high exposure (Table 5).
HEO, heavy equipment operators; JEM, job-exposure matrix; DC, death certificates; MR, medical records.

For each study, we abstracted the following characteristics: country, gender of workers, use of incidence or mortality data for ascertainment of bladder cancer, study design, and adjustment for smoking. We also abstracted the measure of association between diesel exhaust exposure and bladder cancer (odds ratio, rate ratio, standardized mortality ratio, and standardized incidence ratio, thereafter denoted as relative risk [RR]) and their 95% confidence intervals (CIs). In some cases, the RR or the CI was not reported in the publication, but we could derive it from the raw data presented (reported in brackets). When the RR or the CI was not reported and could not be derived, we excluded the study from the review.

We only considered studies for which there were at least 5 years between first exposure to diesel equipment/engines and bladder cancer development. We stratified the studies according to geographic region (Western Europe or North America), study design (cohort, case-control or based on routinely collected data), gender of workers (male or both genders), presence or absence of adjustment for cigarette smoking, and use of incidence or mortality data. We also repeated the review after exclusion of studies based on routinely collected data (*eg* record linkage studies with exposure data derived from census or studies based on death certificates) because of the possible poorer quality of the information on diesel exposure.

We first assessed the number of measures of associations available for each category of exposure. When there were at least five independent results, we assessed the heterogeneity among them, using a meta-regressive approach.[5] When there was limited statistical evidence of heterogeneity, with a *P*-value in excess of 0.1, we conducted a meta-analysis based on a fixed-effects model.[5] We assessed the presence of publication bias using the linear regression approach proposed by Egger *et al.*[6] The meta-analysis was conducted using the STATA programs META, METAREG. and METABIAS.

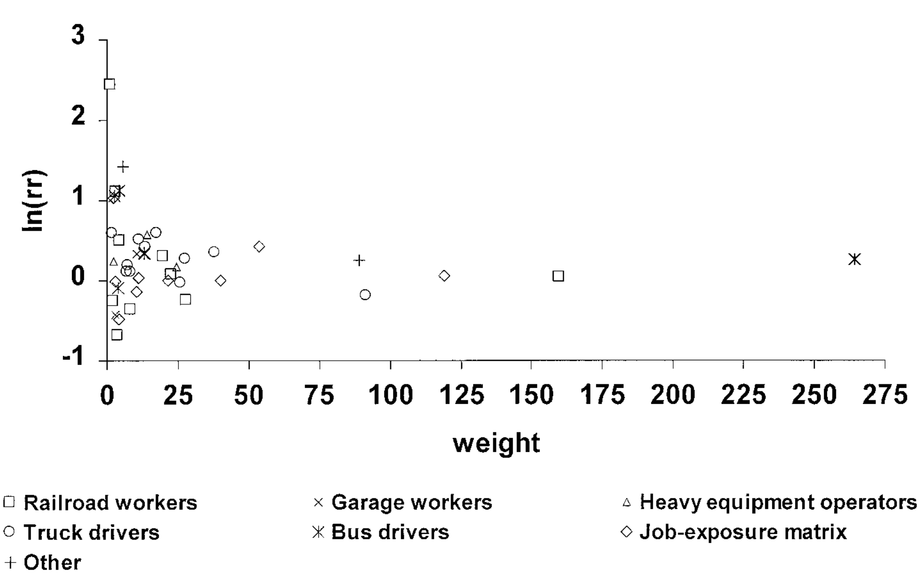

FIGURE 1. Plot of logarithm of relative risk by weight.

Results

We identified 35 studies that provided information on bladder cancer occurrence associated with exposure to diesel exhaust. We excluded three studies because their results were included in larger reports,[7–9] and three more studies because they did not report results for sufficiently specific occupational groups to determine exposure to diesel exhaust (*eg* only transportation workers as a group).[10–12] Of the re-

TABLE 4. Results of the Meta-Analysis

Exposure	N	P-value for Heterogeneity*	RR*	95% CI	Publication Bias P-value
Any exposure	44	0.002			<0.001
Railroad workers	14	0.02			0.6
Garage workers	2				
Heavy equipment operators	5	0.6	1.37	1.05–1.81	0.9
Truck drivers	15	0.3	1.17	1.06–1.29	0.07
Bus drivers	10	0.4	1.33	1.22–1.45	0.001
JEM	10	0.3	1.13	1.00–1.27	0.8

* Meta-analysis performed only for categories with at least 5 results and if P-value > 0.1.
JEM, job-exposure matrix; N, number of studies; RR, relative risk; CI, confidence interval.

maining investigations, seven were cohort studies (Table 1),[13-19] 16 were case-control studies (Table 2),[4,20–34] and six studies were based on routinely collected data (Table 3).[35-40]

Table 4 summarizes the results of the meta-analysis. We obtained 14 results on bladder cancer risk among railroad workers. Although some of the studies suggested an increased RR, some indicated the contrary. The low P-value for heterogeneity (0.02) dictated against a meta-analysis of these data. A total of 15 results were available for truck drivers. Most of the studies reported an increased RR in this group of workers. There was only weak evidence of heterogeneity ($P = 0.3$), so we performed a meta-analysis of these results (Table 4): the summary RR was 1.17 (95% CI = 1.06–1.29). Ten results were available for bus drivers, and most of them suggested an increased RR: we performed a meta-analysis that resulted in a summary RR of 1.33 (95% CI = 1.22–1.45) (Table 4). Relatively few studies were available for the other groups of workers included in our review. For heavy equipment operators, our criteria for performing a meta-analysis were fulfilled and the resulting RR was 1.37 (95% CI = 1.05–1.81) (Table 4). Finally, 10 results were available from studies based on exposure assessment through a job-exposure matrix or a similar approach. Although there were a few positive results, most of them were close to unity. The summary RR was 1.13 (95% CI = 1.00–1.27) (Table 4).

When we considered the 44 independent results of bladder cancer risk from exposure to diesel exhaust, we found strong evidence of heterogeneity among the results ($P = 0.002$) and we did not calculate a summary RR. We obtained similar results for both specific exposure categories and the whole set of results when we excluded from the analysis the studies based on routinely collected data.

Table 4 also reports the results of the analysis on the presence of publication bias. There was a strong indication of the presence of a publication bias in the whole set of 44 independent results. This finding is in agreement with the visual inspection of the results plotted against their standard errors (Figure 1), which suggests a lack of imprecise (small) studies with results below the summary RR. The bias seems to be stronger for studies based on truck or bus drivers than for other groups of studies (Table 4).

The strongest determinant of heterogeneity in the whole set of results was the source of diesel exhaust exposure. This finding supported the choice not to provide a unique summary estimate of the effect of diesel exhaust, and rather to analyze separately groups of studies dealing with different definitions of exposure. In the analysis of groups of studies reporting RRs of bladder cancer in different job titles, none of the characteristics abstracted from the published data seemed to contribute greatly to the heterogeneity of results. Possible exceptions are gender (*ie* results for men, women, or both genders) in the studies of railroad workers and study design in the studies of bus drivers.

Ten studies presented 12 RRs of bladder cancer according to high exposure to diesel exhaust. These results are summarized in Table 5. Since there was no strong evidence of heterogeneity among the eight independent results (P-value 0.5 for the results on exposure at any level reported in Tables 1–3, and P-value 1.0 for the results on high exposure reported in Table 5), we performed a meta-analysis of these data. The meta-analysis resulted in summary RRs of 1.23 (95% CI = 1.12–1.36) for any exposure and 1.44 (95% CI = 1.18–1.76) for high exposure.

TABLE 5. Results on High Exposure to Diesel Exhaust Included in the Meta-Analysis

Study	Exposure	RR	95% CI
Wong *et al*, 1985[16]	20+ years employment as HEO	1.15	0.63–1.92
Boffetta *et al*, 1988[17]	16+ years exposure	0.94	0.32–2.51
Silverman *et al*, 1983[22]	10+ years employment as truck driver	5.5*	NA
Hoar & Hoover, 1985[24]	40+ years exposure	1.7†	0.5–5.0
	20+ years employment as truck driver	1.8	0.8–4.1
Wynder *et al*, 1985[26]	high probability of exposure (JEM)	1.7	0.5–5.3
Silverman *et al*, 1986[4]	truck driver usual employment	1.5	1.1–2.0
	bus driver usual employment	1.5	0.6–3.9
Jensen *et al*, 1987[27]	30+ years employment as bus or truck driver	2.4	0.9–6.6
Kunze *et al*, 1992[31]; Claude *et al*, 1988[7]	30+ years employment as truck driver	3.0*	NA
Siemiatycki *et al*, 1994[33]	high frequency of exposure	1.3	0.8–1.9
Coggon *et al*, 1984[36]	high exposure (JEM)	1.7	0.9–3.3

* Excluded from meta-analysis.
† Overlapping category not used in the analysis of ever exposure to diesel exhaust.
NA, not available; HEO, heavy equipment operators; JEM, job-exposure matrix; RR, relative risk; CI, confidence interval.

Discussion

This review suggests a small increase in the occurrence of bladder cancer among workers exposed to diesel exhaust. The increase seems to be present in all occupational groups included in the analysis. The heterogeneity found among groups of studies with different definitions of diesel exhaust exposure precluded us from providing a summary measure of association. Most results, however, as well as the summary RRs calculated for some exposure circumstances, are compatible with an overall RR on the order of 1.1–1.3.

There are several arguments in favor of a causal relation between diesel exhaust exposure and occurrence of bladder cancer. An increased RR was observed in all groups of studies in which we performed a meta-analysis. Furthermore, out of 12 results for "heavy exposure" (Table 5), 10 were higher than their corresponding results for any exposure (Tables 1–3), and only one of the remaining was lower.[17] The results on dose-response are consistent with data from additional studies that could not be accommodated in the tabular form selected for this review, but are nonetheless relevant. In a case-control study from the United States, the RR of truck drivers was 2.1 (95% CI = 1.2–3.7) (Table 2); truck drivers with self-reported exposure to diesel exhaust had an OR of 11.9 (95% CI = 2.3–61.1).[22] In a Danish cohort of bus drivers, the RRs were higher for workers with 30 or more years of induction time than for other workers.[19]

There are, however, also arguments against a causal interpretation of our results. Confounding by other occupational exposures and by non-occupational factors cannot be completely ruled out. Adjustment for smoking, however, did not explain much of the heterogeneity of the results and the studies with adjustment for smoking in general did not have lower RRs than other studies (Table 2). Other lifestyle factors, such as frequency of urination, might have contributed to the increased occurrence of bladder cancer among drivers, however.[4]

Bias in these data is, in our view, a more serious concern than confounding. We found evidence of publication bias, in particular among the studies of truck and bus drivers. Nevertheless, when we excluded the studies with imprecise results (weight <30, see Figure 1), the summary RR based on the seven large studies of truck or bus drivers was 1.24 (95% CI = 1.16–1.34), as compared with the RR of 1.26 (95% CI = 1.18–1.34) based on the whole set of 27 studies of truck or bus drivers. This result suggests that publication bias does not explain our positive results on drivers.

Preferential report of positive results should always be considered for studies presenting many exposure-disease relations, such as case-control studies of occupational risk factors, and for rare outcomes, such as bladder cancer.

Other potential sources of bias that might have played a role in these studies include: comparison with non-occupational populations, recall bias in case-control studies, and exposure misclassification. It is not possible to assess the impact of these factors on the results we have reviewed. Although it is plausible that their effects might have been in opposite directions, we cannot conclude that their combined effect is likely to have been null.

In conclusion, our review suggested some evidence of a modest increased RR of bladder cancer among workers exposed to diesel exhaust. This result is consistent with biological knowledge on the composition of this mixture, its metabolism and its interaction with the bladder urothelium.[1] The heterogeneity of the results, mainly due to the different definitions of exposure used in the studies, did not allow a meta-analysis, but the effect estimates point toward an overall RR on the order of 1.1–1.3. This result is only slightly lower than the summary RR found in a meta-analysis of lung cancer.[2] The fact that confounding and other biases cannot be excluded as possible explanations for the positive results precludes a causal interpretation.

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